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IN THE U.S. PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

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| Inventor | **Gabor BOGYE** |
| Patent App. | **09/890,029** |
| Filed | **24 July 2001** Conf. No. **6045** |
| For | **PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID** |
| Art Unit | **1617** **Examiner Hui, S** |

Hon. Commissioner of Patents
Box 1451
Alexandria, VA 22313-1451

Appealed 29-Sept-06

APPEAL BRIEF UNDER 37 CFR 41.37

Now comes appellant by his duly authorized attorney and submits his brief under the provisions of 37 CFR 41.37.

(i) REAL PARTY IN INTEREST

The real party in interest is the Appellant Gabor Bogye.

(ii) RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, interferences or judicial proceedings known to Appellant or to the Appellant's legal representative, which may be related to, directly affect, or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Appellant notes that long prior to the filing of this appeal on 29 September 2005,

Appellant had already filed a Notice of Appeal and already paid the fee of $250 using Form PTO 2038. Appellant followed up on 19 July 2005 by filing an Appeal Brief Under 37 CFR 41.37 and paid the fee of $250 again using Form PTO-2038. Upon receiving Appellants's appeal brief the Examiner on 11 October 2005 reopened prosecution of this application and gave Appellant a new office action. In the new office action the Examiner indicated that should Appellant in the future initiate a new appeal, both the Appellant's original payment for filing the notice of appeal and the original payment for filing the appeal brief may be applied to the new, present appeal. Thus no filing fee need accompany the filing of this appeal brief.

(iii) STATUS OF CLAIMS

Claim 1 through 8, 13 through 19, and 21 through 24 have been cancelled.

Claim 9 through 12, 20 and 25 through 39 have been rejected and Appellant appeals the rejection of those claims.

(iv) STATUS OF AMENDMENTS

Appellant filed a Response Under 37 CFR 1,116 After Final Rejection on 4 August 2006 in which no changes were made in the claims, but in which Appellant re-argued for the patentability of all pending claims over the prior art of record. In addition Appellant made of record a number of prior art references in support of his argument that claims 20, 26 through 28, 32, 33, 34, 35 and 36 were clear and definite and in full compliance with the requirements of 35 USC 112, second paragraph. Appellant also reargued that all of the claims in the application were free of the prior art and should not be rejected under either 35 USC 102 as anticipated or under 35 USC 103 as obvious. Appellant received an Advisory Action mailed by the Examiner on 3 October 2006 indicating that the Response Under 37 CFR 1.116 had been considered, but that there were no changes in the rejection of the claims under either 35 USC 112, second paragraph, 35 USC 102 or 35 USC 103.

## (v) SUMMARY OF CLAIMED SUBJECT MATTER

A first feature of the invention as claimed in claim 9 is a method of treating a patient undergoing treatment with a gestagen hormone composition for hormone replacement therapy, for inflammation, for an in vitro fertilization program, for dermatological therapy or for cosmetological treatment to reduce a risk to the patient of thromboembolism induced by taking the gestagen hormone, which comprises the step of administering to the patient simultaneously, previously or subsequently to taking the gestagen hormone composition a therapeutically effective amount of a plasma homocysteine reducing agent. Antecedent basis for this aspect of the invention may be found in the specification on page 3, line 28 through page 6, line 32.

A second feature of the invention as claimed in claim 20is a method of reducing a risk to an otherwise healthy patient of thromboembolism induced by administration of a gestagen hormone to said patient comprising the step of administering to the patient simultaneously, previously or subsequently to taking the gestagen hormone composition a therapeutically effective amount of a plasma homocysteine reducing agent. Antecedent basis for this aspect of the invention may be found in the specification on page 3, line 28 through page 6, line 32, and the first line of Examples a, b, and c on page 7, lines 4 and 19 and page 8, line 3.

A third feature of the invention as claimed in claim 25 is a method of treating a patient taking a composition comprising a gestagen hormone to reduce a risk of thromboembolism induced by taking the gestagen hormone, which comprises the step of administering to the patient simultaneously, previously or subsequently to taking the composition comprising the gestagen hormone, a therapeutically effective amount of Vitamin $B_{12}$, betaine, choline or acetyl cysteine. Antecedent basis for this aspect of the invention may be found in the specification on page 3, line 28 through page 6, line 32.

A fourth feature of the invention as claimed in claim 29 is a method of reducing a risk to an otherwise healthy patient of thromboembolism induced by administration of a gestagen hormone composition to said patient comprising the step of administering to the patient

simultaneously, previously or subsequently to taking the gestagen hormone composition a therapeutically effective amount of a plasma homocysteine reducing agent other than folic acid. Antecedent basis for this aspect of the invention may be found in the specification on page 3, line 28 through page 6, line 32, and Examples a, b, and c, page 7, line 3 to page 8, line 4 especially, page 7, lines 4 and 19, and page 8, line 3.

A fifth feature of the invention as claimed in claim 32 is a method of reducing a risk to an otherwise healthy patient who may be threatened by an elevated plasma homocysteine level as a result of the administration of the gestagen hormone composition which comprises the step of administering to the patient simultaneously, previously or subsequently to the gestagen hormone, a therapeutically effective amount of a plasma homocysteine reducing agent. Antecedent basis for this aspect of the invention may be found in the specification on page 3, lines 28 to the bottom, entire pages, and in the specific examples on pages 7 through 10.

(vi) GROUNDS FOR REJECTION TO BE REVIEWED ON APPEAL

The following issues are to be determined in this appeal:

1. Whether claims 20, 26 through 28, 32 through 35 and 39 should be rejected under 35 USC 112, second paragraph, as vague and indefinite;

2. Whether claims 9, 11, 20, 27, 32, 33, 34, 35 and 36 should be rejected as anticipated under 35 USC 102e or as obvious under 35 USC 103 in view of US Patent 6,190,693 to KAFRISSEN et al;

3. Whether KAFRISSEN et al is an effective prior art reference against any claim on appeal in view of Appellant's submission of a Declaration Under 37 CFR 1.131 during the prosecution of this application;

4. Whether claims 20, 28, 29, 31, 32, 33, 35, 37 and 39 should be rejected under 35 USC 102 as anticipated or under 35 USC 103 as obvious in view of SPELLACY et al;

5. Whether claims 20, 27, 32, 33, 34, 35 and 39 should be rejected under 35 USC

102 as anticipated or obvious under 35 USC 103, in view of BUTTERWORTH et al; and

6. Whether claims 9 through 12, 20 and 25 through 39 should be rejected under 35 USC 103(a) as unpatentable over US Patent 5,654,011 to JACKSON in view of FERMO et al.

(vii) THE ARGUMENTS

Claims 20, 26 through 28, 32 through 35, and 39 should not be rejected under 35 USC 112, Second Paragraph

The Examiner has finally rejected claims 20, 26 through 28, 32 through 35, and 39 under 35 USC 112, second paragraph, as vague and indefinite. The Examiner maintains that claim 39 recites the limitation "for contraception" in line 3 and that there is improper antecedent basis in the claim for this limitation. Appellant disagrees since there is no definite article that is used in front of the expression "for contraception." Furthermore the fact that Appellant deleted in the previous amendment the term "for contraception" from claim 20 does not mean that Appellant is required to maintain this expression in claim 20 to provide antecedent basis for the term in claim 39.

The Examiner further maintains that it is not clear as to who is a healthy patient and whether a patient who suffers side effects such as headache or depression after taking a gestagen hormone is a healthy patient. Appellant disputes that these claims are vague and indefinite.

The term "otherwise healthy patient" in the case of treatment with hormone for contraception defines a patient who is healthy at the beginning of the hormone treatment and remains healthy in the course of the whole treatment. The term "otherwise healthy patient" in indications other than contraception means that apart from the indication of the hormone therapy the patient is healthy at the beginning of the hormone treatment and remains healthy in the course of the whole treatment.

The fact that the patients according to the presently claimed invention remain healthy during the course of the whole treatment is supported by the following:
- The clinical trials disclosed in the present specification are qualified as Phase I trials, which, according to the professional rules, have to be suspended if clinically unexpected effects emerge;
- Also according to the professional rules, any such unexpected effect has to be reported in the summary.

Accordingly, the fact that the Appellant could complete his examinations evidences that his patients remained healthy in the course of the whole treatment. On page 8 in lines 20-21 it is specifically mentioned that "no undesired pregnancy or thromboembolic complication occurred". If any unexpected effect had occurred, it would have been mentioned in the specification.

The term "otherwise healthy patient" is used throughout the relevant technical literature, including US Patents, to define particular patients receiving any number of therapies. For instance in the FERMO et al reference cited by the Examiner, page 1, paragraph 5, and page 3, paragraph 2, describes the test patients as "healthy persons" without any further explanation which indicates that the meaning of the term is well understood by those skilled in the art. Furthermore see the enclosed literature abstracts: J. Clin. Ultrasound 2005, Feb; 33(2): 63 to 66 which mentions "healthy pregnant women" as patients; Dev Med Child Neurol. 1990 Dec: 32(12) 1058 to 1060 which defines the patients as "normal children." See also Eur. J. Echocardiogr. 2005, Jul. 18 which describes treatment of a "healthy population" of patients.

In addition see claim 1 of US Patent 6,562,790 which is directed to a method for abating coronary artery blockage in otherwise healthy male and female human subjects and claim 1 of US Patent 5,855,920 which is directed to a hormone replacement method comprising measuring hormone levels in a sample of an otherwise healthy human's subject blood. Accordingly there is nothing that is at all vague and indefinite about the term "an otherwise healthy patient" used in several of the claims now presented.

Claims 9, 11, 20, 27, 32, 33, 34, 35, and 36 should not be rejected as anticipated under 35 USC 102 or as obvious under 35 USC 103 in view of KAFRISSEN et al.

Appellant's further remarks serve to both establish that the claims on appeal are clear and definite in using the term – otherwise healthy patient - and that claims 9, 11, 20, 27, 32 through 36 and 39 are patentably distinguishable over the KAFRISSEN et al reference and so no rejection of any claim should be maintained as anticipated under 35 USC 102 or as obvious under 35 USC 103 in view of KAFRISSEN et al.

The method of KAFRISSEN et al relates to patients who are afflicted with or predisposed to become afflicted with a disorder due to which they have to be steadily treated with folic acid. This means that the patients of KAFRISSEN et al have to be treated with folic acid independently of the hormone treatment. The present invention, however, relates to healthy patients who do not need folic acid treatment unless they take a gestagen hormone.

In other words, KAFRISSEN el al relates to patients for whom the incidence of certain disorders is higher than normal, while the same for the patients of the invention is non-higher than normal, i.e. normal.

The Examiner argues that an individual having a risk factor can be considered as healthy. Appellant does not agree with this opinion. Although it is agreed that "having the risk factors of a disease is not equal to having the disease itself, but, according to the Appellant, having the risk factors of a disease is not equal to being healthy. Accordingly, individuals can be sorted into three groups: healthy individuals, individuals having the risk factors of a disease, and ill individuals.

In addition, Appellant does not agree with the opinion of the Examiner (last paragraph, page 2), according to which "It is not clear what patients or individuals would be considered "healthy"..., as the term "healthy" is a well-defined one.

The following several references cited provide evidence that the term "healthy" /"otherwise healthy" is clear and unambiguous for one skilled in the art and so the rejection of the claims

under the second paragraph of 35 USC 112, should not be maintained:

According to the definition given in Adipex Phentermine Diet Pills, Diet Pills Glossary of Weight Loss Terms, (2002) appearing on the internet at http://wvvw.adipex-phentermine-dietpills.comfdiet-pills-glossary.asp), "Health is defined as - The overall condition of an organism at a given time in regard to soundness of body or mind and freedom from disease or abnormality."

According to this definition, neither individuals with diseases nor individuals with other abnormalities (e.g. laboratorial abnormality due to which a predisposition can be detected) can be considered as healthy. In other words, those for whom a predisposition for a disease treatable with folic acid can be detected and those for whom no such detection is possible, cannot be both considered as healthy.

In addition, it is clear to a skilled person in the art that the examples of the present application describe clinical pharmaceutical trials (to carry out said trials also clinical-ethical permission had to be procured). Accordingly, the terms "healthy" or "otherwise healthy" have to be discussed in this context, in other words, the question is what these terms mean for a skilled person if they are used in the description of a clinical trial.

According to a document of the National Institute of Health (USA), FAQs About Clinical Studies (copy enclosed), available over the internet at http://clinicaleenter.nih.gov/participate/faqaboutcs.shtml) on page 1, the definition of a healthy volunteer is given as follows:

3. What is a "healthy volunteer"? A volunteer subject with no known significant health problems who participates in research to test a new drug, device, or intervention is known as a "healthy volunteer" or "Clinical Research Volunteer." Accordingly, an individual who has medical problems to be treated with folic acid cannot be considered as healthy.

According to another document of the National Institute of Health, Patient

Information Publications, NIH Clinical Center, (copy enclosed), available over the internet at http://clinicaleenter.nih.gov/participate/-pdf/partners.pdf), the following information about healthy volunteers is given:

"We need to study healthy volunteers for several reasons: ... we need clinical research volunteers to help us define the limits of "normal"."

Accordingly, the group of healthy individuals forms the normal population, and the others can be defined as "higher than normal".

The clinical trials disclosed in the present specification are qualified as Phase I trials. US FDA defines the term "healthy" in the case of Phase I Clinical trials carried out with healthy volunteers according to Phase 1 Clinical Studies, FDA Handbook (copy enclosed) available over the internet at (http://www.fda.gov/cder/handbook/phase1.htm).

"Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."

The next examples show what the term "healthy" means for a skilled person:

FAQs on GCP, Clinical Trial Management, (copy enclosed) and available over the internet at (http://www.clininvent.com/clininvent/links/trial.html)

"What is the US FDA definition of a healthy volunteer?

US FDA guidance on General Considerations for Clinical Evaluation of Drugs discussed this issue. The term "healthy" suggests that a volunteer should be free from abnormalities which could complicate interpretation of the experiment or which might increase the sensitivity of the volunteer to the toxic potential of the drug. A healthy volunteer is one who has no evidence of a clinical biochemical or investigational abnormality (based on physical examination, lab investigations (hematology, liver function, renal function, blood sugar, cholesterol, triglycerides)

and x-ray chest ECG.

US FDA guidance for the industry, "General Considerations for the clinical evaluation of drugs" suggests the following investigations for phase I volunteers..

- CBC including platelet, urinalysis, BUN or creatinine, liver function, FBS or 2 hour postprandial sugar, ECG.
- Any other investigations as per the profile of the drug under investigation. For example, for a study on anti-platelet drug, it would be desirable to check BT, CT, PT in the volunteers. The importance of these tests is two fold. Volunteers should he free from abnormalities which would complicate the interpretation of experiment or which might increase the sensitivity of the subject to the toxic potential of the drug."

According to ABPI (Association of the British Pharmaceutical Industry), Impact of the EU Directive on Ethical Review& Phase 1 Studies, Vol. 14, No. 1, (Feb. 2003) (copy enclosed) and available over the internet at http://archive.instituteofclinicalresearch.org/SMOSubCommittee/Phaseampact.pdfl healthy volunteers can be selected on the basis of full medical history and laboratory tests (page 2, paragraph 4).

According to the homepage of the University of Surrey (Guildford), (copy enclosed) and available over the internet at (http://www.open.mis.surrev.ac.uldmisweb/modules/7431.htm) "Definition of a healthy volunteer (appropriate pre-study test, and considerations of the limits of 'normality' for laboratory data, cardiovascular data)."

Accordingly, the term "healthy" mentioned in the disclosure of the clinical trials in the present application means that at the beginning of the examinations (i.e. at the beginning of the hormone-vitamin treatment) the participants of the trials had no such biochemical abnormality which would have required chronic folic acid treatment (therapeutic or preventive). In other words, the meaning of the term "healthy" in the context of a clinical pharmaceutical trial is well-known for a skilled person: neither those who are afflicted with, nor those who are

predisposed to become afflicted with a disorder due to which they require a continuous (preventive) treatment fall into this category. Obviously, the exact interpretation of the examinations would have been impossible if individuals had been involved who had been given folic acid not only to avoid the side effect of the hormone but they had been in need of folic acid treatment anyway.

Also according to Section 3.2.1. of a document of The European Agency for the Evaluation of Medicinal Products (EMEA), Note for Guidance on the Investigation of Bioavailability and Bioequivalence, and available over the internet at (http://www.emea.eu.int/pdfs/hum an/ewp/140198en.pdf)
healthy volunteers are selected on the basis of medical history and relevant laboratory tests. Therefore, those who are afflicted with, or those who are predisposed to become afflicted with a disorder due to which they require a continuous (preventive) treatment do not fall into this group, as the existing illness or the predisposition can be detected on the basis of the medical history and the relevant laboratory tests.

According to the definition given on the homepage of the International Psoriasis Community, a 501(c)(3) Organization, and appearing on the internet at (http://www.psoriasissupport.org/ipc/default/pnint.asp?laug=1& cont=101) the definition of a "healthy volunteer" is the same as given by the NIH (see above), which evidences the generic and accepted nature of the definition. This site also defines a "patient volunteer": "A volunteer subject with a known health problem, who participates in research to better understand, diagnose, treat, or cure a particular disease or condition."

On the basis of the definitions given for "healthy volunteer" and for "patient volunteer", the patients of KAFRISSEN et al and those of the present invention can be particularly well separated:

| Healthy volunteer | Patient volunteer |
|---|---|
| no known .... health problem | known health problem |
| to test a new drug, device or intervention | to ... cure a particular disease or condition |

Accordingly, for patient volunteers there is a disease to be treated (KAFRISSEN et al), for healthy volunteers there is no known health problem.

According to the information given on the home page of GlaxoSmithKline, (copy enclosed) available over the internet at

http://wvvw.gsk.com/responsibility/cr_issues/ct_healthy_volunteers.htm

"volunteers normally do not have the disease or condition, i.e they are healthy volunteers."

This example shows that the term "healthy" is interpreted by the second largest pharmaceutical company of the world, and, thus, by the skilled person, as including not only the absence of disease, but also the absence of other condition, such as absence of predisposition to become afflicted with a disorder.

According to the official homepage of the US FDA (http://www.fda.gov/) the term "otherwise healthy" is present in 929 documents of the US FDA. From said documents one is selected and enclosed to evidence that the skilled person understands said term according to our interpretation detailed above.

The term "otherwise healthy patient" in indications other than contraception (e.g. in the case of hormone therapy), means that apart from the indication of the hormone therapy the patient is healthy (no other illnesses or predispositions). This definition is well known to those skilled in the art. Appellant points to page 2 of the US Food and Drug Administration, Equality in Clinical Trials Drugs and Gender, Judith Levine Willis,where it is disclosed that a patient infected with HIV is categorized as otherwise healthy.

In response to the questions raised by the Examiner on page 2 of the office action

of 4 May 2006 concerning headache, it is submitted that headache is neither an illness nor a predisposition, but a symptom. A person having a headache may be healthy or may be ill. The question whether someone is healthy or not can be answered on the basis of results of examination and laboratory tests. Patients having normal results are healthy, and patients having abnormal results (e.g. higher than normal) are not healthy.

As for the argumentation of the Examiner in paragraph 1of page 7 of the office action of 4 May 2006, the following is submitted: Comparing males over the age of 65 with younger males, in the first group more individuals are afflicted with prostate cancer or more individuals have risk factors due to which they are predisposed to become afflicted with prostate cancer than in the second group. It does, however, not mean that all male individuals over the age of 65 are afflicted with or become predisposed to become afflicted with said disorder. The question whether someone is healthy or not can be answered on the basis of results of physical examination and laboratory tests. In general, in each age group there is an illness which occurs more frequently than in other age groups; however, it would be a false conclusion drawn from this fact that there exists no healthy individual.

It is believed that on the basis of the references provided it is obvious that those who require a continuous (therapeutic or preventive) folic acid treatment as in KAFRISSEN et al, or those who have diabetes as in SPELLACY et al, or have cervical dysplasia as in BUTTERWORTH et al, cannot be considered healthy. The NIH and FDA references discussed hereinabove unambiguously state that there exist healthy patients and that the term "healthy" cannot be considered indefinite.

The patients of KAFRISSEN et al have to take folic acid in any case, as they are afflicted with or predisposed to become afflicted with a disorder treatable by folic acid. The patients treated according to the presently claimed invention have to take folic acid only if they also must take a gestagen hormone; otherwise they should not take folic acid. Whether a patient falls within the scope of the method of treatment disclosed in KAFRISSEN et al, within the

scope of the presently claimed method of treatment, or within the scope of a third group, can be unambiguously decided on the basis of medical examination and laboratory tests.

Namely, on the basis of said medical examinations and laboratory tests, the patients are grouped into the following groups:

- patients with normal results fall within the scope of the patients treated according to the present invention;

- patients with abnormal results fall within the scope of the KAFRISSEN et al method if the abnormal results show that the individual is afflicted with or predisposed to become afflicted with a disorder treated by folic acid administration; and

- patients with abnormal results, wherein the abnormality is not connected to disorders treated by folic acid belong to a third group.

Thus in the Appellant's view it is not only that his patients treated according to the present method do not fall within the scope of KAFRISSEN et al, but furthermore there is even a third group of patients. In any event there is no disclosure or suggestion in KAFRISSEN et al to administer a plasma homocysteine reducing agent to the particular otherwise healthy patient according to the presently claimed invention to prevent the elevation of the patient's plasma homocysteine levels resulting from administration of a gestagen hormone. Thus none of claims 9, 11, 20, 27, 32 through 36 and 39 should be rejected under 35 USC 102 as anticipated or under 35 USC 103 as obvious in view of this reference.

<u>KAFRISSEN et al is not an effective prior art reference against any claim on appeal view of Appellant's submission of a Declaration Under 37 CFR 1.131.</u>

Appellant turns to the Examiner's refusal to accept the Declaration Under 37 CFR 1.131 that Appellant filed together with his amendment of 9 February 2006. See the Evidence Appendix. Appellant filed the declaration to show that he conceived of the invention well before the effective date of KAFRISSEN et al as a reference under 35 USC 102e and then diligently

reduced his invention to practice. By submitting the evidence of conception of his invention prior to the effective date of KAFRISSEN et al as a reference under 35 USC 102e/103 and of diligent reduction of his invention to practice, Appellant has removed the Examiner's basis for maintaining a rejection of the claims under this section of the statute. Therefore 35 USC 102e/103 should no longer be a basis to apply the KAFRISSEN et al reference against any claim in this application.

Appellant understands that the Examiner has maintained his rejection of claims 9, 11, 20, 27, 32 through 36 and 39 under 35 USC 102e in view of KAFRISSEN et al relying on MPEP 706.02(b)(D)which essentially states that a Declaration Under 37 CFR 1.131 may not be used to antedate an issued US Patent or published US Patent Application where the claims are directed to the same invention or to obvious variants thereof. The Examiner takes the position that the claims of KAFRISSEN et al either overlap with the Appellant's claims or are obvious variants of the Appellant's claims. Appellant disagrees.

Appellant believes that no claim now in the application should be rejected under 35 USC 102e in view of KAFRISSEN et al since the patient treated according to all of the present claims is a different patient from the patient treated according to KAFRISSEN et al. All of the patients treated according to KAFRISSEN et al are patients who are in need of folic acid treatment and so they are not healthy patients. There is no indication even in claims 9 and 11 now presented that the patients treated according to the present invention are not healthy patients. Appellant especially believes that claims 20, 27, 32 through 36 and 39, all directed to a method of reducing a risk in an otherwise healthy patient of thromboembolism induced by administration of a gestagen hormone by administering to the patient a therapeutically effective amount of a plasma homocysteine reducing agent, should not be rejected as anticipated by KAFRISSEN et al, and in fact believes that KAFRISSEN et al is not even an effective reference against these claims.

As explained hereinabove, the patient treated according to KAFRISSEN et al is

not an "otherwise healthy patient" but is a patient whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher than normal incidence. Appellant has explained hereinabove why there is no overlap between the patient defined in KAFRISSEN et al and the patient treated according to the presently claimed invention. Appellant has also explained why it would not be obvious from KAFRISSEN et al to treat the otherwise healthy patient according to the present invention to prevent a risk of thromboembolism according to claims 20, 27, 32 through 36 and 39. Therefore with regard to claims 20, 27, 32 through 36 and 39 there is no reason why the Declaration Under 37 CFR 1.131 should not be accepted and KAFRISSEN et al removed as an effective reference.

Claims 20, 28, 29, 31, 32, 33, 35, 37 and 39 should not be rejected under 35 USC 102 as anticipated or under 35 USC 103 as obvious in view of SPELLACY et al.

SPELLACY et al reference provides no basis to reject claims 20, 28, 29, 31, 32, 33, 35, 37 and 39 now presented as either anticipated under 35 USC 102 or as obvious under 35 USC 103. The patients disclosed in SPELLACY et al are not the same healthy patients that are treated according to the present invention and there is no suggestion in SPELLACY et al to treat the otherwise healthy patients according to the presently claimed method to prevent elevated levels of plasma homocysteine resulting from the gestagen hormone treatment.

The patients of SPELLACY et al became diabetic in the course of the gestagen treatment. On the contrary, as it has been already detailed, the patients of the present invention are healthy - apart from the indication of the hormone therapy - at the beginning of the treatment and remain healthy in the course of the hormone treatment. Diabetes is not an indication of hormone treatment, therefore, the patients of SPELLACY et al and those of the invention are separate.

SPELLACY et al suggests that diabetic patients take Vitamin B6 together with their contraceptive. According to the teaching of the present invention, non-diabetics also have to

take Vitamin B6 together with the contraceptive.

SPELLACY et al does not teach that healthy patients also have to take Vitamin B6 together with the contraceptive, as in the tests disclosed therein the patients who were either already ill with elevated blood glucose levels, or became ill (patient 10) had started hormone therapy already 3-6 months before they started to take also vitamins (page 266, paragraph 3, page 267 paragraph 1, and Table 1 on page 268). In other words, those who were treated with hormone+vitamin were ill patients.

While most of the patients who take contraceptives do not become diabetic as a result of the hormone treatment, in the case of SPELLACY et al, all of the patients became diabetic. This fact suggests that the patients of SPELLACY et al were in fact predisposed to become diabetic even before the start of the treatment solely with the gestagen hormone (without Vitamin B6).

Thus there is no basis to reject any of the claims on appeal as anticipated under 35 USC 102 or as obvious under 35 USC 103 in view of SPELLACY et al.

Claims 20, 27, 32, 33, 34, 35 and 39 should not be rejected under 35 USC 102 as anticipated or obvious under 35 USC 103, in view of BUTTERWORTH et al.

The BUTTERWORTH et al reference provides no basis to reject any of claims 20, 27, 32, 33, 34, 35 and 39 as anticipated under 35 USC 102 or as obvious under 35 USC 103. Reference is made to page 74, Materials and Methods, paragraph 1 of BUTTERWORTH et al according to which "Candidates for study were selected from a population of young women referred to a Public Health Colposcopy Clinic for evaluation of an abnormal cervical smear".

Accordingly, the patients of BUTTERWORTH et al had cervical dysplasia already at the beginning of the folic acid treatment, therefore, they were not healthy. In other words first they were treated solely with a gestagen hormone, due to which they have become afflicted with cervical dysplasia, and afterwards they started to take also folic acid.

According to the last sentence of the abstract, "...such a derangement [in folate metabolism] is an integral component of the dysplasic process that may be arrested (not prevented!) or in some cases reversed by oral folic acid supplementation." Accordingly, in contrast to the opinion of the Examiner, BUTTERWORTH et al does not suggest that healthy patients undertake folic acid treatment for prevention of any disease. This is further confirmed in the Discussion part (page 81, column 2, penultimate line of paragraph 1): "The present study findings suggest that until the situation is further clarified an evaluation of nutritional status regarding folic acid would also be appropriate in patients with early cervical intraephitelial neoplasia."

The patients of BUTTERWORTH et al became afflicted with cervical dysplasia in the course of the hormone treatment. On the contrary, as it has been already detailed, the patients treated according to the presently claimed method are healthy - apart from the indication of the hormone therapy - at the beginning of the treatment and remain healthy in the course of the hormone treatment. Cervical dysplasia is not an indication of hormone treatment, therefore, the patients of BUTTERWORTH et al and those of the invention are separate, and so the reference is not anticipatory. Nor is there any suggestion in BUTTERWORTH et al to treat the otherwise healthy patients according to the present invention with both a gestagen hormone and folic acid. In the advisory action the Examiner himself acknowledged that "it is easy to understand what healthy patients might be". Appellant understands that in this respect the Examiner has changed his mind since the issuance of the final rejection and this revised opinion of the Examiner can be considered as further support of Appellant's argumentation included also in the appeal brief concerning the term "healthy".

In the advisory action the Examiner argues that he gives the broadest reasonable interpretation of the term "otherwise healthy", and, accordingly, he considers the patients of Butterworth also as "otherwise healthy",

because other than the oral contraceptive induced condition, they are healthy. In Appellant's view said interpretation is not broad, but incorrect. This view is supported by the argumentation (and supporting documents) included already in the appeal brief, namely, that in the context of the present patent description a skilled person understands that an otherwise healthy patient is healthy apart from the indication, for which the gestagen was prescribed. Therefore, a patient who became ill (e.g. with cervix dysplasia or diabetes) due to gestagen therapy (which is prescribed e.g. for any of the indications listed in claim 9 or 34) cannot fall into this group, as the gestagen has not been prescribed for cervix dysplasia or diabetes. Gestagens cannot be used for the treatment of cervix dysplasia or diabetes. Thus the patients treated according to BUTTERWORTH et al and treated according to the presently claimed intention are clearly not the same.

Thus no rejection of any claim on appeal should be maintained under either 35 USC 102 or 35 USC 103 in view of BUTTERWORTH et al.

Claims 9 through 12, 20, and 25 through 39 should be rejected under 35 USC 103(a) as unpatentable over US Patent 5,654,011 to JACKSON in view of FERMO et al

The combination of FERMO et al and JACKSON et al is in no way suggestive of the presently claimed method of treatment 9 through 12, 20, and 25 through 39. According to the Examiner, on the basis of the combination of FERMO et al and JACKSON et al the present invention is obvious. FERMO et al discloses only that there is a connection between elevated levels of plasma homocysteine and the development of thrombosis. There is first of all no disclosure or suggestion in either FERMO et al or JACKSON et al to administer a gestagen hormone together with a plasma homocysteine reducing agent. Nor is there any connection disclosed or suggested in either reference of any correlation between elevated plasma

homocysteine levels and administration of a gestagen hormone. Nor is there any indication that administration of a plasma homocysteine reducing agent to an otherwise healthy patient receiving gestagen hormone therapy would prevent thromboembolism in the patient.

Appellant does not agree with the Examiner's conclusion of the obviousness of the present claims in view of these two references in combination and as support for the unobviousness of the present invention, Appellant has made of record in the Response Under 37 CFR 1.116 abstracts of the following references: J. Chromatogr. 1986 , Oct. 31; 382:247-52; Scand J Clin Lab Invest. 1992, Jun; 52(4):283-7; and Obstet Gynecol., 1999, Oct;94(4):485-91. A copy of the Scand J Clin Lab Invest. Article in its entirety was made of record earlier in the prosecution of this application as well. Said documents disclose that hormones do not cause elevated homocysteine levels. Therefore, a skilled person reading FERMO et al and JACKSON et al, either individually or in combination, would conclude that hormone treatment does not effect the homocysteine status of the patient. Thus, it is not suggested to take any homocysteine reducing agent in a hormone treatment.

JACKSON et al suggests the combination of vitamins and minerals for perimenopausal woman in order to prevent or reduce "life stage associated health risks". As taking gestagen hormones is not a life stage associated health risk, it is believed that this citation does not give any guidance to a skilled person to administer to a patient the present method of treatment of the present invention including both a gestagen hormone and a plasma homocysteine reducing agent.

In addition JACKSON et al suggests the administration of 400-440 μg of folic acid, the invention suggests 500 μg to 5 mg.

Appellant would like to draw the attention that, according to page 5, lines 19-26 of the specification, while the plasma homocysteine concentration is diminished by folic acid by 45-50% in hyperhomocysteinaemia of genetic origin (according to the state of the art), it is diminished by 69% in hyperhomocysteinaemia induced by hormones (according to the invention,

see also Example c) on page 8, line 13). In biological systems this difference in the effectiveness of the treatments is considered as significant. Therefore not only was the ability of the plasma homocysteine reducing agents to lower plasma homocysteine levels elevated as a result of taking gestagen hormones surprising in its own right, but furthermore the extent of the effectiveness of reducing plasma homocysteine levels was surprisingly high irrespective of the underlying cause of the plasma homocysteine elevation, including the known underlying genetic cause. Accordingly no rejection of any of these claims should be maintained under 35 USC 103.

In paragraph 3 of page 3 of the Advisory Action of 3 October 2006, the Examiner argues that "a skilled person would have been motivated to employ the homocysteine (HCY) reducing agents to treat the elevated HCY and thereby reduce the risk of thromboembolism, regardless of the cause of the elevated HCY level." Appellant disagrees.

For a person skilled in the art, it is unambiguous that folic acid (and the other HCY reducing agents) are ineffective in most of the thromboembolisms: e.g. thromboembolisms caused by tumor, trauma, immobilization, inflammation, radiation or hypotyreosis. Before the priority date of the present application, namely, 1 February 1999, HCY reducing therapy had not been shown unambiguously effective in any of the thromboembolisms caused by hormones (including other hormones not only gestagens).

Furthermore, as it has been evidenced by the J. Chromatogr. 1986 , Oct. 31; 382:247-52; Scand J Clin Lab Invest. 1992, Jun; 52(4):283-7; and Obstet Gynecol., 1999, Oct;94(4):485-91 references, discussed hereinabove, as of 1 February 1999 it had been believed by those skilled in the art that gestagens or oral contraceptives do not elevate the plasma HCY level. Therefore, in the absence of specific experimental results, the skilled person in the art would not have been motivated to use HCY reducing agents in order to reduce the risk of thromboembolism caused by gestagens. In other words the prior art teaches away from the method of treatment of the invention.

Appellant has found that contrary to the teaching of the prior art, the method of

treatment according to the invention is effective in reducing the risk of thromboembolism caused by administration of gestagens.

As HCY reducing agents arc effective in a very limited fraction of the thromboembolisms, only, the class of HCY reducing agents is a reverse case than that of morphine referred to by the Examiner in the Advisory Action, which has been found to reduce all kinds of pain (with diverse efficiency). Therefore, while, on the basis of the above, the skilled person would not have been motivated to use HCY reducing agents in order to reduce the risk of thromboembolism caused specifically by administration of gestagens, morphine would be expected to be effective against any kind of pain.

Appellant emphasizes that the Examiner did not cite any document which discloses the method of treatment of the invention. If the method of treatment of the invention had been obvious for a skilled person for long time (as it is stated in the Advisory Action), a document disclosing said method of treatment could have been easily cited. Nowhere in the prior art is there either a disclosure of or a suggestion of continued HCY-lowering therapy used explicitly because of HCY-plasma level elevation resulting from gestagen treatment.

For the same reason the argumentation of the Examiner that in the application old and well-known agents are used for known indication (HCY reducing agents for reducing the risk of thrornboembolism), is not correct, as HCY reducing agents are not used for reducing the risk of thromboembolism in general, but only in the case of certain thromboembolisms,

The Examiner's reference to the existence of a monosynapticus reflex on page 4 of the Advisory Action (i.e. if a skilled person sees high HCY (HHCY) then he prescribes HCY reducing agent) is not correct either. According to the above argumentation, it is allowed to order HCY in a certain scope of indications, only. This is, for example, malpractice to order a HCY reducing agent to a patient suffering from hypotyreosis, necessarily having also HHCY, instead of ordering thyroxin.

It is unambiguous from the J. Chromatogr. 1986 , Oct. 31; 382:247-52 that HCY

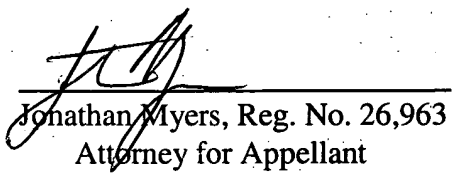
reducing agents are ineffective in most of the thromboembolisms and so it believed that no claim now presented is obvious under 35 USC 103 in view of any of the cited prior art.

Thus no claim on appeal should be rejected under either 35 USC 112, second paragraph; 35 USC 102 or 35 USC 103.

Appellant respectfully requests that the US Patent and Trademark Office Board of Appeals and Interferences reverse the Examiner's rejection of all claims. Appellant has not included any payment for submission of this appeal brief in view of the fact that Appellant already paid the fee for submission of an appeal brief earlier in the prosecution of this application. The fee was paid on 19 July 2005 with the submission of an appeal brief. Following submission of the appeal brief, the Examiner reopened prosecution, and the appeal process was held in abeyance. The Examiner indicated at that time that should the Appellant resume the appeal process, there would be no need to pay once again either the fee for filing a Notice of Appeal or the fee for filing the Appeal Brief.

Since Appellant paid the fee for two Notices of Appeal in the same application, Appellant has requested a refund of the fee paid with the Notice of Appeal filed 29 September 2006. Appellant includes a Document Request for Refund with supporting papers, which is filed concurrently with this Appeal Brief.

Respectfully submitted,
The Firm of Karl F. Ross P.C.



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Enclosures: 131 Declaration & 20 References (listed in evidence appendix)
(previously submitted)
Document request for refund (previously submitted)

(viii) CLAIM APPENDIX

9. A method of treating a patient undergoing treatment with a gestagen hormone composition for hormone replacement therapy, for inflammation, for an in vitro fertilization program, for dermatological therapy or for cosmetological treatment to reduce a risk to the patient of thromboembolism induced by taking the gestagen hormone, which comprises the step of administering to the patient simultaneously, previously or subsequently to taking the gestagen hormone composition a therapeutically effective amount of a plasma homocysteine reducing agent.

10. The method of treatment defined in claim 9 wherein the plasma homocysteine reducing agent is a compound selected from the group consisting of Vitamin $B_{12}$, betaine, choline, and acetylcysteine.

11. The method of treatment defined in claim 9 wherein the plasma homocysteine reducing agent is folic acid.

12. The method of treatment defined in claim 9 wherein the plasma homocysteine reducing agent is Vitamin $B_6$.

20. A method of reducing a risk to an otherwise healthy patient of thromboembolism induced by administration of a gestagen hormone to said patient comprising the step of administering to the patient simultaneously, previously or subsequently to taking the gestagen hormone composition a therapeutically effective amount of a plasma homocysteine reducing agent.

25. A method of treating a patient taking a composition comprising a gestagen hormone to reduce a risk of thromboembolism induced by taking the gestagen hormone, which comprises the step of administering to the patient simultaneously, previously or subsequently to taking the composition comprising the gestagen hormone, a therapeutically effective amount of Vitamin $B_{12}$, betaine, choline or acetyl cysteine.

26. The method of reducing a risk of thromboembolism defined in claim 20 wherein the plasma homocysteine reducing agent is a compound selected from the group consisting of Vitamin $B_{12}$, betaine, choline, and acetylcysteine.

27. The method of reducing a risk of thromboembolism defined in claim 20 wherein the plasma homocysteine reducing agent is folic acid.

28. The method of reducing a risk of thromboembolism defined in claim 20 wherein the plasma homocysteine reducing agent is Vitamin $B_6$.

29. A method of treating a patient undergoing treatment with a gestagen hormone composition to reduce a risk to the patient of thromboembolism induced by taking the gestagen hormone composition, comprising the step of administering to the patient simultaneously, previously or subsequently to taking the gestagen hormone composition, a therapeutically effective amount of a plasma homocysteine reducing agent other than folic acid.

30. The method of treatment defined in claim 29 wherein the plasma homocysteine reducing agent is a compound selected from the group consisting of Vitamin $B_{12}$, betaine, choline, and acetylcysteine.

31. The method of treatment defined in claim 29 wherein the plasma homocysteine reducing agent is Vitamin $B_6$.

32. A method of reducing a risk of thromboembolism upon administration of a gestagen hormone to an otherwise healthy patient who may be threatened by an elevated plasma homocysteine level as a result of the administration of the gestagen hormone composition which comprises the step of administering to the patient simultaneously, previously or subsequently to the gestagen hormone, a therapeutically effective amount of a plasma homocysteine reducing agent.

33. The method of reducing a risk of thromboembolism defined in claim 32 wherein the otherwise healthy patient is from a class of individuals whose plasma homocysteine levels have been elevated by administering to the patient a gestagen hormone composition and where the patient's plasma homocysteine level is reduced following administration of the plasma homocysteine reducing agent.

34. The method of reducing a risk of thromboembolism defined in claim 33 wherein the patient has been administered the gestagen hormone composition for contraception, for hormone replacement therapy, for inflammation, for an in vitro fertilization program, for dermatological therapy or for cosmetological treatment.

35. The method of reducing a risk of thromboembolism defined in claim 33 wherein the plasma homocysteine reducing agent is selected from the group consisting of folic acid, Vitamin $B_6$, Vitamin $B_{12}$, betaine, choline, and acetylcysteine.

36. The method of reducing a risk of thromboembolism defined in claim 9 wherein the plasma homocysteine reducing agent is folic acid administered in an amount of 0.5 to 5 mg/day.

37. The method of reducing a risk of thromboembolism defined in claim 29 wherein the plasma homocysteine reducing agent is Vitamin $B_6$ administered in an amount of 10 to 300 mg/day.

38. The method of reducing a risk of thromboembolism defined in claim 29 wherein the plasma homocysteine reducing agent is Vitamin $B_{12}$ administered in an amount of 300μg to 5 mg/day.

39. The method of reducing a risk of thromboembolism defined in claim 20 wherein the gestagen hormone is administered to the patient for contraception or for hormone replacement therapy.

## (ix) EVIDENCE APPENDIX

Appellant enclose a copy of a Declaration Under 37 CFR 1.131. The declaration was submitted by Appellant together with his amendment of 9 February 2006 and was entered by the Examiner and considered by the Examiner on page 8 of the office action mailed 5 May 2006.

Appellant encloses copies of the following references submitted during the prosecution of this application to show that there was no known connection at the time that the present invention was made between the administration to a patient of a gestagen hormone and the elevation of blood plasma homocysteine levels as a result of taking the gestagen hormone. In fact it was believed at the time of the present invention that administration of a gestagen hormone to a patient had no effect on the plasma homocysteine level of the patient.

1. U.S. Patent 5,855,920; 5 Jan. 1999; Edmund Chein
2. U.S. Patent 6,562,790; 13 May 2003; Edmund Chein
3. J. Clin. Ultrasound, Feb. 2005, 33 - I. Kocijancic; Sonographic detection of physiologic pleural fluid in normal pregnant women
4. WO 00/51596; 8 Sept. 2000; Messadek
5. GlaxoSmithKline: Healthy volunteer studies (www.gsk.com)
6. Diet Pills Glossary of Weight Loss Terms (www.adipex-phentermine-diet-pills.com)
7. NIH Clinical Center: FAQ About Clinical Studies (www.clinicalcenter.nih.gov)
8. Phase 1 Clinical Studies (www.fda.gov)
9. ClinInvent: Clinical Trial Management (www.clininvent.com)
10. Impact of the EU Directive on Ethical Review & Phase 1 Studies; Vol. 14; No. 1; Feb. 2003

11. EMEA: Committee for Proprietary Medicinal Products; 26 July 2001 (www.eudra.org)
12. International Psoriasis Community (www.psoriasissupport.org)
13. Patient Information Publications NIH Clinical Center: Partners in Research
14. www.open.mis.surrey.ac.uk - Full Module Description
15. U.S. Food and Drug Administration: Equality in Clinical Trials Drugs and Gender Judith Levine Willis FDA Consumer Special Report
16. J. Chromatogr. 1986 Oct. 31; 382:247-52: Analysis of homocysteine in human urine using high-performance liquid chromatography with electrochemical detection (abstract only)
17. Scand J Clin Lab Invest. 1992, Jun; 52(4):283-7 (abstract and full text)
18. Obstet Gynecol. 1999, Oct;94(4):485-91 (abstract only)
19. Dev Med Child Neurol. 1990 Dec: 32(12)
20. Eur. J. Echocardiogr. 2005 July 18

It is noted that references 1 through 4, 19 and 20 were entered by the Examiner together with Appellant's Amendment filed 9 February 2006;

It is noted that references 5 through 16, 17 in abstract form, and 18 were entered by the Examiner together with the Appellant's Response After Final Rejection filed 4 August 2006.

## (x) RELATED PROCEEDINGS APPENDIX

There have been no decisions rendered by a court or by the Board of Appeals and Interferences in a related proceeding and no such proceeding has been identified in the Related Appeals and Interferences Section of the Appeal Brief.